UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,994	05/03/2001	Kristiina Ylihonko	1574/49884	7174

23911 7590 08/11/2004

CROWELL & MORING LLP
INTELLECTUAL PROPERTY GROUP
P.O. BOX 14300
WASHINGTON, DC 20044-4300

EXAMINER	
KERR, KATHLEEN M	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 08/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,994	YLIHONKO ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-5 and 9-16* is/are pending in the application.

4a) Of the above claim(s) *4,5 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3 and 9-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-final rejection (mailed on February 11, 2004), Applicants filed a response and amendment received on July 8, 2004. Said amendment cancelled Claim 1, amended Claims 2, 3, 9, 12, 13, and 15 and added new Claim 16. Thus, Claims 2-5 and 9-16 are pending in the instant Office action.

2. Receipt of Applicant's declaration under 35 U.S.C. § 1.132 on July 8, 2004 is acknowledged.

Election

3. Claims 2-5 and 9-16 are pending. Claims 4-5 and new Claim 16 are withdrawn from consideration as non-elected inventions. Claims 2, 3, and 9-15 will be examined herein.

The restriction requirement was previously made final. Applicant is invited to file a petition under 37 C.F.R. § 1.144 for review of the restriction requirement (see M.P.E.P. § 821).

For completeness herein and to aid any decision by the Office in deciding an appropriately filed petition of the restriction requirement, the Examiner will respond to Applicant's arguments. Applicant argues that each of the genes in the disclosed gene cluster for the biosynthesis of aclacinomycins are not "functional alone" due to overlapping open reading frames. The Examiner disagrees. Despite any overlapping reading frames, distinct genes are found throughout the full-length gene cluster. Moreover, the function of their encoded proteins act independently of one another. As noted by Raty *et al.* (Gene (2002) 293: 115-122) in

description of the *S. galilaeus* aclacinomycin polyketide synthase (PKS) gene cluster, such a type II PKS contains "several discrete polypeptides, each carrying a distinct activity, loosely associated in a complex" (see page 115). Thus, the Examiner maintains that the distinct genes in the gene cluster, encoding distinct enzymes, render the parts (the discrete genes) different from the whole (the gene cluster) in both structure and function since SEQ ID NO:14 is not equivalent to a portion of SEQ ID NO:14 and since producing aclacinomycin is not equivalent to producing an intermediate along the aclacinomycin biosynthetic pathway.

Applicant further argues that the gene cluster, as a whole, is more useful. The Examiner has already conceded such a point – this does not render moot the Examiner's argument for lacking unity of invention. Applicant's argue that the cluster should be examined in its entirety; this is exactly the case in examining the instant claim 2, drawn to the entire cluster and sequence related to this full-length sequence (not portions thereof). The lack of unity of the complete gene cluster with the individual parts of the gene cluster does not prohibit Applicant from being his/her own lexicographer. Applicant is invited to file divisional applications to pursue every invention defined by the Examiner in the previous written restriction requirement. The Examiner maintains that the written restriction of record is coextensive with all the different inventions described in the instant application.

If upon reading the response above, Applicant maintains that "[t]he present restriction is precisely the type of degradation of Applicants' statutory right which the law does not permit", Applicant is invited to file a petition of the restriction requirement as is proper under 37 C.F.R. § 1.144.

Priority

4. As previously noted, the instant application is granted the benefit of priority for the International Application No. PCT/FI00/00819 filed on September 25, 2000 foreign application 19992085 filed on September 29, 1999. Applicant has provided a copy of the claims from the foreign priority document missing from the instant U.S. application; said claims recite 84% homology to SEQ ID NO:14.

Withdrawn - Objections to the Specification

5. Previous objection to the specification for lacking clarity in its examples is withdrawn by virtue of Applicant's explanation on the record in their remarks.

Withdrawn - Objections to the Claims

6. Previous objection to Claims 2-3 and 9-15 for being drawn to non-elected subject matter is withdrawn by virtue of Applicant's amendment deleting all non-elected subject matter from the claims.

Withdrawn - Claim Rejections - 35 U.S.C. § 112, second paragraph

7. Previous rejection of Claims 1, 3, and 9-15 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "anthracycline biosynthetic pathway" is withdrawn by virtue of Applicant's amendment deleting this term from the claims.

8. Previous rejection of Claim 3 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "**the** DNA fragment of claim 2" (emphasis added) is withdrawn by virtue of Applicant's amendment.

9. Previous rejection of Claims 12 and 15 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "metabolites" is withdrawn by virtue of Applicant's amendment to the term "polyketide" which is well-known in the art.

Maintained - Claim Rejections - 35 U.S.C. § 112, second paragraph

10. Previous rejection of Claims 2, 3, and 9-15 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "84% homology" is maintained. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicant argues that the above term is clear by means of a declaration filed under 35 U.S.C. § 1.132. The declaration under 37 C.F.R. § 1.132 filed July 8, 2004 is insufficient to overcome the rejection of claims 2,3, and 9-15 under 35 U.S.C. § 112, second paragraph, because the declaration does not clarify what the term "homology" means in the instant claims. As previously noted, "Is this meant to be 84% identity over the full-length of SEQ ID NO:14? In the art, homology can apply to highly homologous portions of sequences. Thus, the metes and bounds of the term are unclear." The declaration describes a complicated and less-than-accurate means for estimating the amount of identity that the full-length gene cluster (SEQ ID NO:14) has with the prior art using amino acid (encoded fragments of the full-length sequence) identities, wobble-base assumptions, and averages over a broad range of 39-77% identity at the amino acid level; the means for identifying the claimed homology has not clarified the term whatsoever.

Applicant further argues that identity searches are routine in the art; the Examiner does not disagree. As previously questioned, is the term "homology" more broad than the term identity, which term has a clear definition in the art? Clarification is required.

11. Previous rejection of Claim 13 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "anthracycline metabolites" is maintained. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicant argues that because the term "anthracycline metabolites" is found three published Abstracts, the term would be clear to one of skill in the art. The Examiner disagrees. Despite the term's use in the prior art, the definition of said term is open to interpretation by one of skill in the art. The Abstracts cited by Applicant do not define all the compounds encompassed by the term "anthracycline metabolites". Anthracyclines are large compounds with numerous possible metabolites. How similar to anthracycline must the metabolite be? Must the metabolite be produced by some natural circumstance or can *any* reaction that alters an anthracycline produce an anthracycline metabolite? Most striking support for the Examiner's rejection is found in Applicant's own support for the clarity of the term – in the abstracts of both Yoshimoto *et al.* in J. Antibiotic (1993) 46(1): 56-64 and Yue *et al.* in J. Bacteriol. (1986) 2:581-586 wherein "new anthracycline metabolites" are produced in mutant *Streptomyces* strains. Thus, a compound that might not have been considered an anthracycline metabolite prior to the production of these mutant strains would now, by Applicant's definition of being "known in the art", be considered an anthracycline metabolite. With such a flexible definition, the metes and bounds must clearly be defined in terms of structural relatedness for the term to be clear. Clarification is required.

12. Previous rejection of Claims 14 and 15 under 35 U.S.C. § 112, second paragraph, as being indefinite for the terms "activator" and "polyketide assembler" is maintained. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicant argues that the term "activator" means "a gene product which activates expression of genes in the biosynthetic cluster by binding DNA in the promoter sequence"; however, the Examiner cannot read such limitations into the claims, particularly when such limitations are not described in the specification as originally filed. Moreover, the claim language is even unclear as to whether or not the "activator" is a protein since the language reads "wherein the DNA fragment includes an activator". For these reasons, the term is not clear.

Applicant argues that the term "polyketide assembler" means "an enzyme related to the assembling of a polyketide chain" and that its use in the review article of Hopwood *et al.* clearly defines the term. The Examiner can find no occurrence of the term "polyketide assembler" in the referenced article. While assembling polyketides is described in the article, no single polypeptide is described as being responsible for such an activity. Thus, the term is unclear as used in the instant claims.

Withdrawn - Claim Rejections - 35 U.S.C. § 112, first paragraph

13. Previous rejection of Claims 1 and 9-15 under 35 U.S.C. § 112, first paragraph, written description, is withdrawn by virtue of Applicant's amendment removing all fragment language from the claims.

Maintained - Claim Rejections - 35 U.S.C. § 112, first paragraph

14. Previous rejection of Claims 2, 3, and 9-15 under 35 U.S.C. § 112, first paragraph, written description, is maintained. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicant argues that because the fragment language has been deleted from the claim, the instant rejection no longer applies; this is not the case. As previously noted by the Examiner:

> "The instant specification discloses a DNA fragment encoding polypeptides necessary to produce aclacinomycins in a heterologous host cell; **this DNA fragment of SEQ ID NO:14**. Applicants have fully described the genus relating to said SEQ ID NOs with both sequence identity limitations and functional limitations. However, the genus of the instant claims also contains DNA fragments within the sequence identity limitations, but having different function. Applicants have not fully described a genus that has sequence identity limitations in the absence of functional limitations." (emphasis added)

The "fragment" used throughout the previous rejection refers specifically to the sequence that is SEQ ID NO:14. Thus, the rejection was previously set forth because a DNA fragment (sequence) having 84% identity to SEQ ID NO:14 but having different function was encompassed by the claim language but not described in the specification. This portion of scope has not been excluded from the claim language with amendment. Thus, the instant rejection is maintained. The Examiner suggests inserting functional language to describe "a sequence showing at least 84% homology to said sequence" to overcome the instant rejection.

15. Previous rejection of Claims 2, 3, and 9-15 under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for the DNA fragment that is SEQ ID NO:14, does not reasonably provide enablement for polynucleotides with such low sequence homology, such as the 84% claimed, is maintained. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicant argues, "the stated 84% homology is high, not low, as alleged by the Examiner. For example, polyketide cyclase SnoaM is 73% and 71% homologous to AknW and DpsY,

respectively. The genes of all of these three enzymes are able to complement non-producing S. peucetius mutant D2 to produce daunomycins." Firstly, the Examiner notes that "SnoaM" is likely sga10 of the instant specification, which is a discrete gene in the gene cluster that is SEQ ID NO:14, since a cyclase activity is mentioned in Applicant's arguments; if this assumption is in error, the Examiner requests clarification on the record. More importantly, the "homology" described in response is for a single gene of the gene cluster, not for the entirety of SEQ ID NO:14 which is being claimed in the instant claims. Additionally, the ability to complement is not coextensive with having the same function of the protein; for example, a mutant in an enzyme of beginning steps of a biosynthetic pathway might be complemented by a protein that up-regulates (by means of activation, addition copies, mutation to a more active enzyme) a previously "slow" member of the same pathway downstream in the pathway.

Even if the level of % homology described by Applicant is indicative of similar sequences encoding proteins having the same activity, the specifics of which residues within the 16% (100-84%) of variability allowed by the claim breadth is not enabled. While one of skill in the art may be able to find all related sequences using hybridization and screening techniques, one of skill in the art would be unable to make all such sequences without a clear understanding of which residues are crucial to the aclacinomycin-biosynthetic nature of SEQ ID NO:14. Since ability to make is a requirement of the statute, this understanding of the nature of SEQ ID NO:14 and its possibility variability is crucial to enable the claim to the full extent of its scope.

16. Previous rejection of Claims 9, 11, and 14 under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods of increasing aclacinomycin production and/or producing metabolites in a Streptomyces host that naturally

produces aclacinomycins, does not reasonably provide enablement for methods of increasing or producing in all Streptomyces hosts is maintained. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicant argues that the claims, as amended, require the host cells to produce aclacinomycins or intermediates thereof and that this obviates the rejection; the Examiner disagrees. While the phrase "producing aclacinomycins" alone would obviate the rejection, as indicated in the first line of the previously stated rejection, the claim also includes *Streptomyces* host cells that merely produce aclacinomycin intermediates. Firstly, this term is unclear as noted below in the new rejection under 35 U.S.C. § 112, second paragraph. Secondly, just because a *Streptomyces* makes aclacinomycin intermediates does not mean that it can now make aclacinomycin as required by the method claim, particularly in light of the lack of a functional requirement for the DNA fragment of Claim 2. For these reasons, Applicant's amendment has not overcome the instant rejection; the rejection as explained in the previous Office action is maintained. The following is an excerpt from the previous office action for completeness:

> "The instant specification teaches a gene cluster containing 13 genes described as encoding enzymes involved in aclacinomycin biosynthesis; most activities of these encoded proteins are "deduced" according to homologous sequence in databases (although these homologous sequences are not disclosed) (see Table 1 on page 12 of the specification). Only 9 genes, those encompassed by Sg4, are used in complementation assays to assign functionality putatively. Only Sg4 is transformed into S. peuceticus and S. galilaeus to increase aclacinomycin production. Thus, no description of using the entire gene cluster in any Streptomyces host cell to make aclacinomycins is taught. Moreover, from the figures, it is clear that SEQ ID NO:14 does not comprise all the genes necessary to make a complete anthracycline; said genes participate in the production of the sugars attached to the aklavinone structure. One of skill in the art would be unable to predict if SEQ ID NO:14 contains the entire gene cluster capable of producing aclacinomycins in a heterologous host (that is, one that does not produce aclacinomycin naturally). Thus, one of skill in the art would be unable to practice the claimed methods in all Streptomyces host cells. Claim 11 is included

in the instant rejection because no limitation of the derivation from S. galilaeus is in the claim, thus, the mutant used could be one that does not natively produce aclacinomycins."

Withdrawn - Claim Rejections - 35 U.S.C. § 102

17. Previous rejection of Claims 2, 3, and 9-15 under 35 U.S.C. § 102(a) as being anticipated by Raty *et al.* is withdrawn by virtue of Applicant's completing the foreign priority document (19992085 filed in Finland) by filing the certified copy of the claim set. The instant claims are now afforded an earliest effective filing date of September 29, 1999 rendering Raty *et al.* no longer prior art.

NEW ISSUES

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claims 9-11, 13 and 14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "intermediates" as referring to aclacinomycin intermediates is unclear. Without a clear pathway for the biosynthesis of aclacinomycin, the nature of intermediates along said pathway are wholly unclear. Clarification is required.

Other Art of Record

19. The following is made of record by the Examiner has having been considered:

a) Tsukmoto *et al.* Cloning of Aklavinone Biosynthesis Genes from *Streptomyces* galilaeus. Journal of Antibiotics (1992) 45(8): 1286-1294.

Summary of Pending Issues

20. The following is a summary of the issues pending in the instant application:

a) Claims 2, 3, and 9-15 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "84% homology".
b) Claims 9-11, 13 and 14 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "intermediates".
c) Claim 13 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "anthracycline metabolites".
d) Claims 14 and 15 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the terms "activator" and "polyketide assembler".
e) Claims 2, 3, and 9-15 stand rejected under 35 U.S.C. § 112, first paragraph, written description.
f) Claims 2, 3, and 9-15 stand rejected under 35 U.S.C. § 112, first paragraph, scope of enablement (breadth of 84% homology).
g) Claims 9, 11, and 14 stand rejected under 35 U.S.C. § 112, first paragraph, scope of enablement (breadth of using non-aclacinomycin-producing *Streptomyces*).

Conclusion

21. Claims 2, 3, and 9-15 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

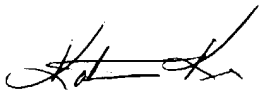
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R.

§ 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Kathleen M Kerr
Examiner
Art Unit 1652

August 6, 2004